STUDIES OF THE ACUTE AND CHRONIC TOXICITY OF UNDECYLENIC ACID*

G. W. NEWELL, PH.D., A. K. PETRETTI, M.D. AND L. REINER, M.D., PH.D.

In a recent paper by Perlman (1) undecylenic acid, administered orally, was suggested as a therapeutic agent for psoriasis, neurodermatitis, and associated arthropathies. Undecylenic acid and its salts, however, have been used for a number of years as successful topical agents in the cure of various fungous infections of the skin (2, 3, 4).

Little work has been reported in the literature on the metabolism or toxicity of undecylenic acid. Artom and Swanson (5) have shown that as little as 1.1–2.9 gm of the ethyl ester of undecylenic acid caused death in 150 gm rats in 45–90 minutes, when given orally. Verkade and van der Lee (6) reported that large doses of triglyceride of undecylenic acid caused nephritis in humans. When this glycerol ester was included at a 5% level in a semi-purified ration and fed to rats, the animals developed paralytic seizures and died in 2–3 hours (Ozaki, 7).

Inasmuch as the reported clinical success with undecylenic acid in psoriasis involved the use of large doses, it was considered important to determine the toxicity of this substance. The results of the experiments comprise data on acute toxicity studies of undecylenic acid with mice and preliminary results of chronic experiments with rats which were fed purified rations containing varying amounts of undecylenic acid.

EXPERIMENTAL

Acute Toxicity

Male and female mice of the Carworth CF_1 strain, weighing 18–22 gm, were used in the oral and intraperitoneal acute toxicity tests. Preliminary results indicated that there was no difference in sensitivity between males and females. Male mice were thus used in the majority of the experiments. Before administration of the acid, the animals were starved for 12–18 hours and then maintained on a commercial ration during the following 72 hours of observation. In the oral studies, undecylenic acid was diluted with sesame oil to a constant volume of 0.35 cc and force fed with the aid of a blunted, curved #24 needle. In the intraperitoneal studies, undecylenic acid was diluted with sesame oil to a constant volume of 0.50 cc. A highly purified sample of ω-undecylenic acid, with an acid number of 305 (theoretical value: 304), was used in all these experiments.

Data obtained after oral administration and intraperitoneal injection of undecylenic acid are shown in Table I. When the acid was fed orally, a dose causing death in 50 per cent of the mice ($L.D._{50}$) lay between 0.136 and 0.181 gm. These results were submitted to statistical analysis as suggested by Bliss (8),

* From the Research Department, Wallace & Tiernan Products, Inc., Belleville, New Jersey.

Received for publication May 19, 1949.

based upon small numbers of values as modified by Miller and Tainter (9) by plotting data on log-probit paper. In the same manner, the $L.D._{50}$ for 18 gm mice was found to be 0.147 ± 0.031 gm of undecylenic acid fed orally (8.15 gm/kg).

When the acid was given intraperitoneally, deaths occurred between the doses of 0.011 to 0.024 gm. From these values the $L.D._{50}$ dose was calculated to be 0.0173 ± 0.00013 gm of undecylenic acid for 18 gm mice or 0.960 gm/kg.

At the dose levels between 0.136–0.290 gm a number of mice died within one to two hours after the feeding. The animals first showed hyperirritability, ran about the cage, occasionally jumping spasmodically. Immediately before death, the animals went into a state of shock-like collapse. Upon autopsy, it was found that the majority of animals showed engorgement of the stomach and of the proximal portion of the small intestine, with occasional petechial hemorrhages,

TABLE I

Acute Toxicity of Undecylenic Acid on Mice (Oral)

NO. OF ANIMALS	UNDECYLENIC ACID (G)	MORTALITY (72 HRS.)
3	0.034	0/3
3	0.068	1/3
4	0.091	1/4
10	0.102	2/10
6	0.109	3/6
12	0.136	5/12
8	0.181	5/8
4	0.290	3/4
	(Intraperitoneal)	
6	0.011	1/6
6	0.016	0/6
6	0.020	5/6
6	0.024	6/6
6	0.036	6/6

and with what appeared to be liquefactive necrosis of the mucosa. In almost all cases the heart stopped in systole. Microscopic studies will be carried out on the organs of the animals now on the chronic toxicity experiments and will be reported on in a subsequent communication.

The effect of injecting large volumes of sesame oil was found to be negligible. Six mice injected with 0.5 cc of sesame oil, the maximum volume used in the above experiments, were alive and symptomless at the end of 72 hours. Similarly, 0.35 cc of sesame oil given orally had no effect on six 18 gm mice at the end of the 72 hour test period.

Oleic acid, an unsaturated fatty acid which is a constituent of commonly consumed fats, was used in an attempt to determine what effect high doses of known non-toxic acids might have when administered to young mice. Oleic acid injected in the same volume as the maximum used of undecylenic acid caused death to one animal in 48 hours. When given orally at the highest level used of

undecylenic acid, oleic acid caused the death of one animal in 24 hours. Six animals were used per group and the same diluents and volumes were employed as in the previous experiments.

TABLE II

	R-8	R-9	R-10	R-13	R-14	R-15
Glucose	69%	69%	69%	69%	69%	69%
Casein	20	20	20	20	20	20
Salts IV	4	4	4	4	4	4
Whole Liver Powder	2	2	2	2	2	2
Corn Oil	5	2.5	2.5	4	4	4.5
Oleic Acid		2.5		1		
Undecylenic Acid			2.5		1	0.5

The following vitamins were added per kg of ration: thiamine HCl, 2 mg; riboflavin, 3 mg; pyridoxine HCl, 3 mg; niacin, 6 mg; Ca pantothenate, 20 mg; and choline Cl, 1 g. One drop of halibut liver oil administered orally per rat per week.

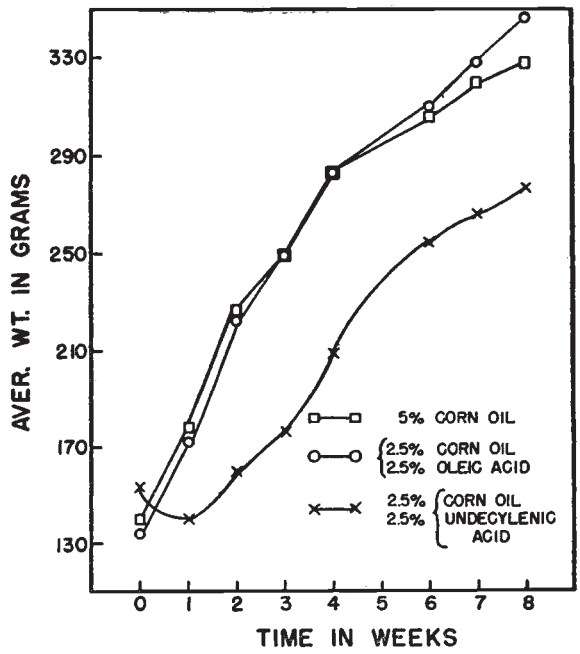

FIG. I. Growth response of rats fed, *Ad Libitum*, purified rations, containing undecylenic acid.

Chronic Toxicity

Male rats of the Sprague-Dawley strain, weighing about 150 gm were used in the chronic toxicity studies. Composition of the rations is given in Table II. Corn oil and purified oleic acid were used as controls. In the first experiment, food and water were fed *ad libitum* and undecylenic acid was fed at the level of

2.5% of the ration. Figure I shows the results of feeding, *ad libitum*, purified rations containing either 2.5% of corn oil and 2.5% of oleic acid or 2.5% of corn oil and 2.5% of undecylenic acid, as compared to rations containing 5% of corn oil. The immediate drop in weight of animals fed undecylenic acid was followed by a gradual recovery period so that the growth response was about parallel for each group after the fourth week.

Since the odor and taste of undecylenic acid might have caused decreased food consumption, resulting in the decreased growth of the animals (Figure I), it was decided to pair feed several additional groups of animals at lower levels of unde-

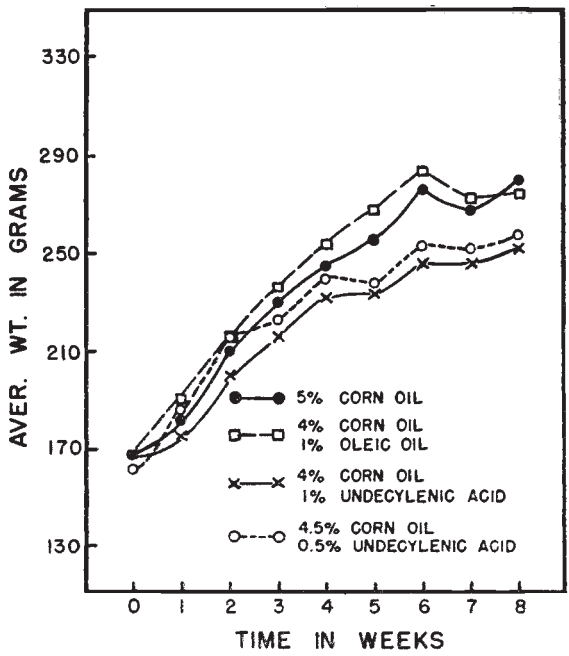

FIG. II. Growth response of rats fed purified rations containing undecylenic acid under conditions of paired feeding.

cylenic acid. The method of paired feeding involves daily limitation of food intake by all groups to the smallest amount of food consumed by one particular group the day before. In this experiment, four groups of 150 gm male rats, 7 per group, were pair fed throughout the experiments; the effects produced by 1% and 0.5% of undecylenic acid in the ration were compared to that of 1% of oleic acid and of corn oil alone. Figure II shows the results of pair feeding these rations. Although 1% of undecylenic acid had an inhibitory effect the first week on the rate of growth, 0.5% of undecylenic acid did not show a marked retardation until after the fourth week. After the fifth week the rate of growth was about equal in all groups. Both chronic toxicity tests are being continued and will be reported in the future.

SUMMARY

Studies have been conducted on the acute and on the chronic toxicity of ω-undecylenic acid. An oral dose which will cause death in 50% of the mice tested ($L.D._{50}$) has been determined as 8.15 ± 1.7 gm/kg. The intraperitoneal $L.D._{50}$ dose for mice was found to be 0.960 ± 0.007 gm/kg.

Chronic toxicity studies have shown that a ration containing 2.5% undecylenic acid, fed *ad libitum*, has a marked inhibitory effect on the growth of rats. When paired feeding studies were instituted and the undecylenic acid included at 1% or 0.5% of a ration, the inhibition of growth was reduced, but there was still a definite retardation of growth.

REFERENCES

1. Perlman, H. H. Undecylenic Acid in Psoriasis and Neurodermatitis. J.A.M.A., **139:** 444–447, Feb. 12, 1949.
2. Shapiro, A. L. and Rothman, S. Undecylenic Acid in the Treatment of Dermatomycosis. Arch. Dermat. & Syph., **52:** 166–171, 1945.
3. Sulzberger, M. B., Shaw, H. C., and Kanof, A. Evaluation of Measures for Use against Common Fungous Infections of Skin, Screening Tests by Means of Paired Comparisons on Human Subjects. U. S. Nav. M. Bull., **45:** 237–248, 1945.
4. Hopkins, J. B., Fisher, J. F., Hillegas, A. B., Ledin, R. B., Rebell, G. C., and Camp, E. Fungistatic Agents for Treatment of Dermatophytosis. J. Invest. Dermat., **7:** 239, 1946.
5. Artom, C. and Swanson, M. The Action of Bromo-Substituted Fatty Acids on Liver Fat. J. Biol. Chem., **148:** 633–639, 1943.
6. Verkade, P. E. and van der Lee, J. Fat Metabolism. V. Some Experiments on Man on the Breakdown of Unsaturated Fatty Acids. Z. Physiol. Chem., **230:** 207–212, 1934.
7. Ozaki, J. The Relative Nutritive Value of Synthetic Fats. Biochem. Z., **177:** 156–167, 1926.
8. Bliss, C. I. Determinations of Dosage-Mortality Curve from Small Numbers. Quart. J. Pharm. & Pharmacol., **11:** 192–216, 1938.
9. Miller, L. C. and Tainter, M. L. Estimation of the $L.D._{50}$ and its Error by Means of Logarithmic-Probit Graph Paper. Proc. Soc. Exper. Biol. & Med., **57:** 261–264, 1944.